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Invited Review

Molecular genetics of ovarian carcinomas

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Summary. The phenotypic variability of epithelial ovarian neoplasms correlates with a diversity of changes at the molecular level. Invasive serous and undifferentiated ovarian carcinomas are characterized by p53 mutations with p53 protein accumulation, extensive loss of genetic material of chromosome 17 and complex changes on many other chromosomes, e.g. amplification of oncogenes. These alterations are seen only in a minority of mucinous and endometrioid carcinomas, mainly in advanced stages. Overexpression of bcl-2 is seen most frequently in endometrioid carcinomas (ca. 90% of cases), which in addition show microsatellite instability in around a third of the cases, as has been described in endometrioid endometrial carcinomas. KRAS mutations are characteristic for mucinous LMP tumors and mucinous carcinomas (40-50% of cases) and are also found in a third of serous LMP tumors. In addition, serous LMP tumors show mild microsatellite instability in 30%. However, complex chromosomal aberrations are never seen in these neoplasms.

Key words: Ovarian carcinoma, Molecular genetics, Molecular pathology

Introduction

Epithelial ovarian neoplasms are thought to arise from the ovarian surface epithelium and its inclusion cysts. The different phenotypes of these tumors reflect the various differentiation patterns of the Mullerian epithelium of the female genital tract. The serous (tubal), mucinous (endocervical) and endometrioid type are the three types encountered most frequently. Most undifferentiated ovarian carcinomas probably represent dedifferentiated serous carcinomas (Russell, 1994). Epithelial ovarian neoplasms are further subclassified into benign, borderline and malignant tumors according to their degree of proliferation, cytological atypia and the presence or absence of stromal invasion. The biological position of the non-invasive borderline tumors, also called tumors of low malignant potential (LMP), is still unclear. At present there is controversy as to whether LMP tumors represent a precursor lesion of invasive carcinomas or a distinct entity developing through a separate molecular pathway (Russell, 1994).

The biological behavior of the various forms of epithelial ovarian tumors differs considerably. 5-year survival rates of LMP tumors are above 90%. Comparable data for invasive carcinomas show a correlation to the histological type. In our own Munich study collective, treated between 1985 and 1992 5-year survival for endometrioid carcinoma was 67%, for mucinous carcinomas 62%, for serous carcinomas 34% and for undifferentiated carcinomas 23% (Diebold et al., 1996a). However, it has to be taken into account that endometrioid and mucinous carcinomas are relatively often diagnosed in FIGO stage I, whereas most serous and undifferentiated carcinomas are advanced stage carcinomas at the time of surgery (FIGO II or III) (Diebold et al, 1996a).

Recent molecular pathological studies have improved our understanding of the molecular basis of ovarian carcinogenesis. It has been shown that the phenotypic differences between the various forms of epithelial ovarian neoplasia correlate with different changes at the molecular level (Pieretti et al., 1995; Diebold et al., 1996a,b, 1997b). This review summarizes the characteristic changes of the main types of epithelial ovarian tumors. The description focuses on invasive carcinomas and LMP tumors, because only few data are available for adenomas. Furthermore, only those studies which have taken the histological tumor type into account will be discussed.

Invasive serous carcinomas

Multiple tumor cytogenetic and molecular genetic alterations are found in advanced serous and undifferentiated ovarian carcinomas. These alterations are associated with gross changes of the nuclear amount of DNA, reflected by DNA non-diploidy in DNA cytometry (Table 1). Serous and undifferentiated tumors show the highest proliferative activity of all types of epithelial ovarian neoplasms (Table 1).

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Table 1. Results obtained in our laboratory

	Ki67 >10%	DNA NON-DIPLOIDY	p53 ACCUMULATION	Bcl-2 EXPRESSION
S-LMP	0/22 (0%)	2/22 (9.1%)	0/23 (0%)	10/23 (43.5%)
SC	26/64 (40.6%)	54/68 (79.4%)	36/69 (52.2%)	40/69 (58%)
UC	8/11 (72.7%)	10/11 (90.9%)	8/11 (72.7%)	8/11 (72.7%)
M-LMP	0/7 (0%)	0/6 (0%)	0/7 (0%)	0/7 (0%)
MC	1/18 (5.6%)	7/17 (41.2%)	5/18 (27.8%)	5/18 (27.8%)
EC	7/12 (58.3%)	7/15 (46.7%)	3/15 (20%)	13/15 (86.7%)
p-value	< 0.001	< 0.001	< 0.001	= 0.001

S-LMP: serous tumors of low malignant potential; SC/UC: serous and undifferentiated carcinomas; M-LMP: mucinous tumors of low malignant potential; MC: mucinous carcinomas; EC: endometrioid carcinomas. p-value according to chi^2-test.

In highly differentiated serous carcinomas conventional tumor cytogenetics mainly reveals numerical aberrations (most frequently +12, +8, +7), whereas most moderately or poorly differentiated carcinomas harbor complex karyotypes with numerical aberrations (mainly +12, +20, -X, -22, -17, -13, -8) and numerous structural changes. The chromosomal bands or segments most often affected by structural aberrations are (in decreasing order) 19p13, 1p36, 1q21, 1q23-25, 3p11-13, 6q21, 19q13, 11p13-15, 11q13, 11q23, 12q24, 12p11-13 and 7p13-22 (Pejovic, 1995; Mertens et al., 1997). Tumor metaphases often contain marker chromosomes that cannot be defined by conventional cytogenetics.

Analyses of polymorphic microsatellite loci (mostly by PCR) have revealed loss of heterozygosity (LOH) on many chromosomes, most frequently involving 17p (60-75%) (Tavassoli et al., 1993; Osborne and Leech, 1994; Pieretti et al., 1995; Wertheim et al., 1996; Saretzki et al., 1997), 17q (50-65%) (Eccles et al., 1992; Jacobs et al., 1993; Tavassoli et al., 1993; Osborne and Leech, 1994; Pieretti et al., 1995; Wertheim et al., 1996; Saretzki et al., 1997), 6q (42-75%) (Lee et al., 1990; Sato et al., 1991, 1992; Foulkes et al., 1993b; Orphanos et al., 1995), 6p (27%) (Foulkes et al., 1993b), 11q (57%) (Foulkes et al., 1993a), 11p (43-46%) (Lee et al., 1990; Osborne and Leech, 1994), 13q (56%) (Sato et al., 1991; Dodson et al., 1993; Cheng et al., 1996), X (40%) (Yang Feng et al., 1993; Osborne and Leech, 1994; Cheng et al., 1996), 22 (65%) (Bryan et al., 1996), 19 (45-67%) (Sato et al., 1991; Osborne and Leech, 1994), 18 (60%) (Chenevix Trench et al., 1992), 9 (48-89%) (Osborne and Leech, 1994; Devlin et al., 1996), 15q (40%) (Dodson et al., 1993; Osborne and Leech, 1994) and 14q (46%) (Osborne and Leech, 1994).

By use of comparative genomic hybridization (CGH) genetic changes were predominantly found in poorly differentiated serous ovarian carcinomas. Chromosomal gains were seen on 1q22-31 (in 31% of cases), 3q25-26 (50%) and 8q24 (58%) and chromosomal losses on 16q (38%) and 17pter-q21 (46%) (Iwabuchi et al., 1995).

If one compares the results of the different methods mentioned, it becomes evident that the new molecular genetic data only partially match the conventional tumor cytogenetic results. Overall the following lesions seem to be particularly relevant: loss of parts or the whole chromosome 17; partial loss of chromosome 6; and alterations on chromosome 11. On chromosomes 3, 8, 12 and 20 oncogenes relevant to ovarian carcinogenesis have been described (Iwabuchi et al., 1995). The significance of alterations of chromosomes 1, 7, 9, 13, 14, 15, 18, 19, 22 and X has not been clarified. Most of these changes probably do not represent early changes, but are non-specific lesions associated with tumor progression.

Chromosomes 6 and 11 are particularly interesting, because they contain important hormone receptor genes: the progesterone receptor gene on 11q22 and the estrogen receptor gene on 6q25.1. Although early stages of ovarian carcinogenesis are probably hormone dependent (Dietl and Marzusch, 1993), the receptor genes mentioned are not part of the frequent aberrations on chromosome 6 and 11. The minimal region deleted on chromosome 6 has been mapped to 6q27 (Saito et al., 1992).

In addition, chromosome 11 contains the locus of the cyclin D1 gene on 11q13, which is a regulator of the G1 check point of the cell cycle. In advanced (FIGO stage III) serous ovarian carcinomas increases of the cyclin D1 gene can be found. Furthermore, the chromosomal region 20q13 can also demonstrate copy changes (Iwabuchi et al., 1995). Both alterations are associated with poor prognosis (Diebold et al., unpublished observations). On 20q13 the CAS gene apparently involved in the regulation of apoptosis has been identified (Brinkmann et al., 1996). In the vicinity, on 20q12 the AIB1 gene, a steroid receptor coactivator, has been found which is frequently amplified in conjunction with 20q13 (Anzick et al., 1997).

Regarding the number of genes relevant to tumor biology, chromosome 17 is probably the best characterized chromosome. Alterations of the tumor suppressor gene p53 on 17p13.1 are of pivotal importance for serous ovarian carcinomas. Allelic loss of p53, which may be part of larger chromosomal deletions, and p53 mutations are frequent and have been found in up to 87% of cases (Mazars et al., 1991; Okamoto et al., 1991; Kohler et al., 1993; Kupryjanczyk et al., 1993; Milner et al., 1993; Kappes et al., 1995; Kim et al., 1995). 80-90% of p53 mutations lead to the production of an immunohistochemically detectable p53 protein with increased stability and prolonged half-life-time (Kupryjanczyk et al., 1993). p53 protein accumulation can be seen in 50-73% of serous and undifferentiated ovarian carcinomas

and has prognostic relevance (Table 1) (Bosari et al., 1993; Henriksen et al., 1994; Renninson et al., 1994; Diebold et al., 1996a).

Nevertheless, p53 mutations are apparently not early genetic lesions in ovarian carcinogenesis, in particular for two reasons: 1) because p53 accumulation and mutations are only rarely found in stage FIGO I cases; and 2) because ovarian carcinomas do not belong to the spectrum of malignancies which frequently develop in families with p53 germ line mutation (Buller et al., 1995; Kleihues et al., 1997).

The oncogene ERBB2 (17q21.1) and the tumor suppressor gene BRCA1 (17q21) are two other important genes on chromosome 17. 89% of ovarian carcinomas found in families with BRCA1 germ line mutation belong to the serous or undifferentiated type (Rubin et al., 1996). Analysis of apparently sporadic ovarian carcinomas has revealed BRCA1 mutations in around 5% of cases (Takahashi et al., 1995; Merajver et al., 1995; Stratton et al., 1997).

Immunohistochemically, the ERBB2 receptor has been detected in 6% to 43.7% of serous carcinomas and with similar frequency in other histological types of ovarian carcinomas (Haldane et al., 1990; Rubin et al., 1994; Singleton et al., 1994; Fajac et al., 1995). The wide range is due to the lack of standardization of ERBB2 immunohistochemistry. Apparently, there is no correlation between ERBB2 receptor expression and ERBB2 gene amplification in ovarian carcinomas (Fajac et al., 1995). In contrast to older reports (Slamon et al., 1989) true ERBB2 gene amplification is seemingly a rare event in ovarian carcinomas (Persons et al., 1993; Fajac et al., 1995) which agrees well with the fact that the whole chromosome 17 is often deleted (Tavassoli et al., 1993).

The genes on chromosome 17 are of paramount importance for the stability of the genome. Extensive loss of chromosomal material of chromosome 17 is associated with high frequency of LOH and DNA copy changes detectable by CGH on other chromosomes (Iwabuchi et al., 1995; Pieretti et al., 1995). Furthermore p53 accumulation correlates with cytometrical DNA non-diploidy (Diebold et al., 1996c).

MYC, KRAS and BCL2 are genes on other chromosomes which are relevant to serous ovarian carcinomas. Gain of chromosomal material of the long arm of chromosome 8 regularly includes the MYC locus at 8q24. MYC is often amplified in ovarian carcinomas. However, this phenomenon does not correlate with the histological type (Diebold et al., 1996c).

Around 15% of serous ovarian carcinomas harbor mutations at codon 12 of the KRAS oncogene on chromosome 12p12.1 (Mok et al., 1993; Teneriello et al., 1993; Ichikawa et al., 1994; Pieretti et al., 1995). Furthermore, a fraction of serous and undifferentiated carcinomas show strong expression of the bcl-2 oncoprotein (Table 1). The gene of this antiapoptotic protein is located on 18q21.3. Bcl-2 protein is regularly found in non-neoplastic surface epithelium of the ovary (Henriksen et al., 1995). Bcl-2 expression in ovarian carcinomas is associated with favorable prognosis (Marx et al., 1997). In particular, p53-positive carcinomas which coexpress bcl-2 have a better prognosis than p53 positive cases without strong bcl-2 expression (Diebold et al., 1996a). In contrast, carcinomas which express bax (a partner of bcl-2) and are bcl-2-negative have a significantly adverse outcome (Marx et al., 1997).

A relatively new class of tumor suppressor genes encompasses genes that are involved in DNA mismatch repair. Loss of function of these genes plays a central role in HNPCC ("hereditary non-polyposis colon cancer"). So far, mutations in mismatch repair genes have not been found in serous ovarian carcinomas (Fujita et al., 1995). This agrees well with the fact that microsatellite instability in dinucleotide repeats is only rarely seen in this tumour type (0-9%) (Fujita et al., 1995; King et al., 1995; Pieretti et al., 1995; Tangir et al., 1996).

Serous LMP tumors (borderline tumors)

Serous LMP tumors are distinguished from invasive serous carcinomas by several features. They develop 10 to 15 years earlier, by definition do not show stromal invasion and have an excellent prognosis. Conventional tumor cytogenetic data are scarce for these tumors. Interphase cytogenetic analysis indicates that serous LMP tumors can harbor numerical chromosomal aberrations. In serous LMP tumors as well as in serous carcinomas centromeric gain of chromosome 6 and 7 has been revealed (Diebold et al., 1996b). The results of these studies are compatible with the hypothesis that serous borderline tumors are precursor lesions of invasive serous carcinomas.

However, molecular genetic investigations show profound differences between these tumors. One difference concerns microsatellite instability. Tangir et al. (1996) and our own study group (Diebold et al., 1997a) found this phenomenon in upto 65% of serous LMP tumors. However, in most cases it was observed at only one locus. Instability at two or more loci is seen in 30%. In contrast, only mild microsatellite instability was seen in serous carcinomas analyzed in comparison. The significance of this observation is not completely clear at present, but it has been postulated that even mild MI may contribute to carcinogenesis (Shakney and Shankey, 1997). Whether mutations in DNA mismatch repair genes are responsible for this phenomenon is not known.

Around a third of serous LMP tumors harbor mutations at codon 12 of the oncogene KRAS (Mok et al., 1993; Teneriello et al., 1993; Ichikawa et al., 1994; Pieretti et al., 1995; Haas et al., unpublished observations). Thus, the frequency of this aberration is twice as high as in invasive serous carcinomas. In contrast, loss of heterozygosity and alterations of the oncogenes (ERBB2, MYC) and tumor suppressor genes (p53) mentioned above are rarely or never found in serous LMP tumors (Teneriello et al., 1993).

Like ovarian surface epithelium about half of serous borderline tumors strongly express bcl-2 protein. Furthermore, one group of investigators has suggested that an important tumor suppressor gene is located on the X chromosome. However, this remains to be clarified (Cheng et al., 1996).

The observations concerning microsatellite instability and KRAS mutations indicate that at least in a fraction of serous borderline tumors different tumorigenic mechanisms are at work compared to invasive serous carcinomas. This may explain why the transformation of an LMP tumor to a clearly malignant carcinoma occurs so rarely (Kurman and Trimble, 1993).

Future studies will have to clarify whether the subgroup of LMP tumors which have been called "micropapillary serous carcinomas" (Burks et al., 1996; Seidman and Kurman, 1996) and which may represent cases with adverse prognosis differs at the molecular level from other LMP tumors.

Mucinous neoplasms

Mucinous ovarian neoplasms have significantly less tumor cytogenetic and molecular genetic alterations than serous tumors. This is the reason for the smaller number of cases that are DNA cytometrically non-diploid (Table 1).

Due to the comparatively smaller number of tumor cells and the low proliferative activity (see Table 1) only few mucinous ovarian neoplasms have been analyzed by conventional tumor cytogenetics. In most cases either a normal karyotype or only a few aberrations were found (Pejovic et al., 1992). Some moderately or poorly differentiated mucinous carcinomas possessed complex karyotypes (Tanaka et al., 1989; Thompson et al., 1994a). However, using interphase cytogenetics it has been shown that the majority of cytometrically DNA diploid mucinous tumors contain chromosomal aberrations. Gain of centromeric signals of chromosome 1 was the most prevalent finding which could be seen even in some mucinous adenomas (Diebold et al., 1997b).

The smaller number of chromosome 17 changes in mucinous carcinomas is one main difference to serous carcinomas. Loss of heterozygosity on chromosome 17 is seen in a third of mucinous carcinomas. However, multiple LOH, which would indicate loss of larger parts of chromosome 17, has been never observed (Eccles et al., 1992; Jacobs et al., 1993; Pieretti et al., 1995). Interphase cytogenetics demonstrating loss of centromer-17-signals significantly less often in mucinous than in serous carcinomas, agrees well with allelotype (LOH) studies (Diebold et al., 1997b). Immunohistochemical p53 accumulation is detected in 25-30% of mucinous carcinomas (Bosari et al., 1993; Henriksen et al., 1994; Renninson et al., 1994; Diebold et al., 1996a). The low frequency of chromosome 17 changes is associated with a smaller overall number of LOH on other chromosomes (Foulkes et al., 1993a; Pieretti et al., 1995; Bryan et al., 1996; Devlin et al., 1996). For example, LOH on 6q is seen in less than 10% of cases (Saito et al., 1992; Orphanos et al., 1995).

Microsatellite instability is apparently not important in mucinous neoplasms, since it is detected in less than 10% of cases (Fujita et al., 1995; Pieretti et al., 1995; Tangir et al., 1996). In contrast, KRAS mutations are very prevalent in these tumors and surpass the frequency of this alteration in serous LMP tumors. Combining the results of larger studies, 47% of mucinous LMP tumors and 44% of mucinous carcinomas have KRAS mutations (Teneriello et al., 1993; Mok et al., 1993; Ichikawa et al., 1994; Pieretti et al., 1995; Cuatrecasas et al., 1996).

Endometrioid carcinomas

Moderately or poorly differentiated endometrioid carcinomas harbor complex cytogenetic aberrations like serous carcinomas (Jenkins et al., 1993). Only highly differentiated carcinomas can have less complex karyotypes (Thompson et al., 1994b). LOH is seen in advanced endometrioid carcinomas in similar frequency as in serous carcinomas: 6q (50-70%) (Foulkes et al., 1993b; Orphanos et al., 1995), 17 (23-69%) (Eccles et al., 1992; Shenson et al., 1995; Saretzki et al., 1997), 11q (2/4=50%) (Foulkes et al., 1993a), 9 (4/4=100%) (Devlin et al., 1996) and 22q (45%) (Bryan et al., 1996).

p53 accumulation is detected in 20-55% of cases (Bosari et al., 1993; Henriksen et al., 1994; Renninson et al., 1994; Diebold et al., 1996a). In our own study all p53-positive carcinomas were in FIGO stage II or III. LOH analysis of chromosome 17 and p53 immunohistology, therefore, suggest that loss of p53 function is associated with tumor progression of endometrioid carcinomas (Pieretti et al., 1995). Relatively few cases have been investigated for microsatellite instability which could be detected in 10-50% (Fujita et al., 1995; King et al., 1995; Pieretti et al., 1995; Shenson et al., 1995). Probably the exact frequency is in the range of 30%. This agrees well with the figure which has been reported for microsatellite instability in endometrioid endometrial carcinomas (Kobayashi et al., 1995), which belong to the spectrum of malignancies in the HNPCC syndrome. In a few cases of endometrioid ovarian carcinomas, underlying mutations in a mismatch repair gene (hMSH2) have been detected (Fujita et al., 1995).

Like proliferating endometrial glands (Gompel et al., 1994) endometrioid ovarian carcinomas almost always show strong expression of the antiapoptotic bcl-2 oncoprotein (Table 1). KRAS mutations are found in 21% of ovarian carcinomas of this type (Mok et al., 1993; Teneriello et al., 1993; Ichikawa et al., 1994; Pieretti et al., 1995).

Synoptic view of phenotype and molecular genetics of ovarian carcinomas

Table 2 summarizes the present knowledge about the molecular genetic alterations in ovarian carcinomas. It becomes evident that some carcinogenetic mechanisms

are preferentially but not exclusively associated with certain histological tumor types. This suggests that the patterns described cannot be the sole cause of the phenotypic variability of epithelial ovarian neoplasms. It seems more likely that these patterns are instead responsible for the different biological behavior of these tumors. The aggressive course of serous and undifferentiated carcinomas correlates with extensive changes on chromosome 17 and multiple alterations on other chromosomes. In mucinous and endometrioid carcinomas, which behave more favorably, these changes are far less frequent. For mucinous neoplasms, KRAS mutations are particularly characteristic. Overall, an inverse correlation between KRAS mutations and the finding of multiple LOH in the genome exists (Pieretti et al., 1995). Regarding endometrioid carcinomas it remains to be elucidated whether the antiapoptotic action of bcl-2 protein is of particular carcinogenetic relevance.

The favorable prognosis of serous LMP tumors may be correlated with two tumorigenetic mechanisms: KRAS mutations and microsatellite instability which can be mild or (in a few cases) widespread. Interestingly, in colon carcinomas microsatellite instability is associated with better prognosis. Mild microsatellite instability in serous LMP tumors is probably caused by different mechanisms to microsatellite instability in endometrioid

Table 2. Frequency of microsatellite instability (MIN), KRAS mutations, p53 mutations and loss of chromosome 17 and loss of heterozygosity (LOH) at multiple loci in relation to the histological type of epithelial ovarian neoplasms (our results and literature, see text).

	MIN	KRAS	p53 MUTATION/ LOOS OF CHR. 17	LOH AT MORE THAN 3 LOCI
S-LMP	++*	++	-	-
SC/UC	(+)	+	++	++
M-LMP	(+)	++	-	-
MC	(+)	++	+	-
EC	+	+	+ (> FIGO I)	+

S-LMP: serous tumors of low malignant potential; SC/UC: serous and undifferentiated carcinomas; M-LMP: mucinous tumors of low malignant potential; MC: mucinous carcinomas; EC: endometrioid carcinomas. Frequency: -, 0%; (+), 1-10%; +, 11-30%; ++, >30% of cases; *: mostly mild MIN.

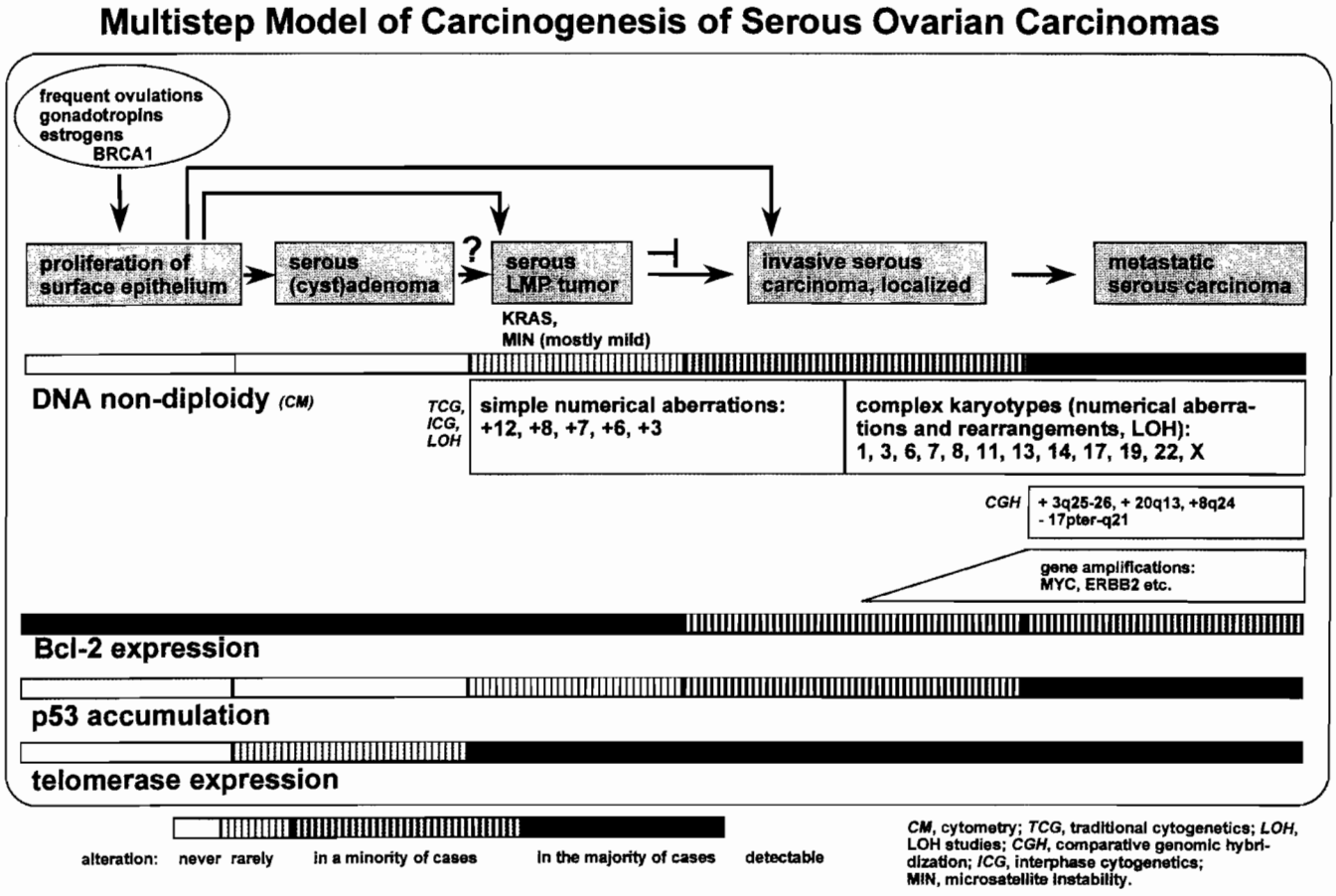

Fig. 1. Molecular pathological multistep model of the carcinogenesis of serous ovarian carcinomas. Two possible pathways are depicted: 1, transformation of serous adenomas into serous LMP tumors and progression to invasive serous carcinomas; 2, de-novo-development of serous LMP tumors and carcinomas.

carcinomas which belong to the HPNCC-associated malignancies. As in colon carcinomas, ovarian neoplasms with microsatellite instability possess relatively few additional genetic lesions (Schlegel et al., 1995).

Loss of function of the tumor suppressor p53 is a pivotal marker for tumor progression of the various forms of epithelial ovarian neoplasia. It has been hypothesized that the selection process for tumor cell clones with defective p53 is driven by the dependence of tumor growth on angioneogenesis (Levine, 1997). Normal, i.e. wild type p53 inhibits neovascularization via the action of thrombospondin. In addition, hypoxia activates normal p53 and thereby induces apoptosis. Therefore, inactivation of p53 seems to be a crucial step in tumor progression which ensures continuous tumor growth. The low frequency of p53 alterations in serous LMP tumors and mucinous neoplasms may thus explain the relatively poor vascularization in these tumors, whereas the high frequency of p53 mutations and p53 protein accumulation in serous and undifferentiated carcinomas indicates that these neoplasms are mainly detected in advanced stages of tumor development.

LOH analyses, CGH and interphase cytogenetics have shown that the genomic alterations in ovarian carcinomas are distributed in a non-random manner. This is probably also caused by evolutionary pressure that leads to the selection of tumor cell clones with characteristic genetic patterns which perhaps correspond to the functional characteristics of the ovary.

In contrast to tumor progression the early phases of ovarian carcinoma development are poorly understood. Reexpression of the "immortalization" enzyme telomerase is not only seen in advanced ovarian carcinomas, but also in serous LMP tumors and in some serous cystadenomas (Counter et al., 1994; Wan et al., 1997) . DNA hypomethylation is found in carcinomas as well as in LMP tumors; however, its role in the process of neoplastic transformation needs to be clarified (Cheng et al., 1997).

To what extent ovulation frequency and hormonal disturbances are involved in ovarian carcinogenesis has not been answered. Furthermore, the earliest mutations that lead to neoplastic transformation have not been elucidated. KRAS mutations and microsatellite instability may represent early genetic lesions that are sufficient for neoplastic transformation, but not for tumor progression. However, as shown above, these alterations are only rarely found in invasive serous carcinomas, the most frequent type of ovarian carcinomas.

Figure 1 depicts a carcinogenetic multistep model which summarizes the knowledge about the molecular alterations in serous ovarian neoplasms. However, it must be realized that the existence of an adenoma-LMP tumor-carcinoma sequence has not been proven for the ovary. Such a sequence is supported by epidemiological data, a few case reports and the results of interphase cytogenetics which show very similar numerical chromosomal aberrations in LMP tumors and carcinomas. Furthermore, the preferential expression of bcl-2 in LMP tumors and early-stage serous carcinomas on the one hand and the correlation between p53 alterations and advanced tumor stages on the other hand are compatible with a multistep model. However, they do not prove it. In contrast, the inverse relation between microsatellite instability and LOH in serous LMP tumors and serous carcinomas argues against an adenoma-carcinoma-sequence. The reexpression of telomerase in LMP tumors and carcinomas is compatible with both views, if one considers that telomerase is found in most malignant human tumors.

Conclusions

Molecular pathological studies have provided new insights into the molecular basis of ovarian tumors. The correlation between phenotype and patterns of molecular alterations can partially explain the different biological behavior of the various forms of epithelial ovarian neoplasms. Although such analyses are not yet part of the routine diagnostic evaluation of ovarian tumors, the results show that a meticulous histological classification is of pivotal importance for optimal clinical patient care. The main aim should be to distinguish the different types of invasive carcinomas and to identify non-invasive LMP tumors.

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